Ultraviolet Radiation-induced Immune Modulation: Potential Consequences for Infectious, Allergic, and Autoimmune Disease

MaryJane K. Selgrade,[1] Michael H. Repacholi,[2] and Hillel S. Koren[1]

[1]National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711 USA; [2]World Health Organization, Geneva 27, Switzerland

Both the U.S. Environmental Protection Agency (EPA) and the World Health Organization (WHO) are concerned with potential health effects that might result from increased exposure to ultraviolet radiation (UVR) as a result of depletion of stratospheric ozone by anthropogenic chemicals such as chlorofluorocarbons and halons. Major targets for UVR effects include the skin, eye, and immune system. A thorough review of effects of UVR on these tissues was published recently by WHO (*1*). In 1989, the EPA's Health Effects Research Laboratory (HERL, predecessor of NHEERL, the National Health and Environmental Effects Laboratory) convened an expert panel to identify research needs to improve health risk assessments with respect to UVR exposure. At that time there were sufficient data to make quantitative estimates of the risks of skin cancer and cataract development associated with depletion of stratospheric ozone. Studies also indicated that some immune functions were compromised by exposure to UVR and that this might influence the incidence and severity of infectious diseases as well as vaccine effectiveness. However, data necessary to quantitate the risk to the immune system were not available. As a result of recommendations from the expert panel, HERL initiated a small, focused research effort to improve this data base. The need to accurately assess the risk of UVR exposure to the immune system is critical, since these effects are expressed immediately, in contrast to skin cancer and cataracts, which take years to develop. In 1994, HERL and the UV Monitoring and Assessment Program, an industrial group, held a workshop that focused on potential effects UVR- induced immune suppression might have on infectious disease in humans and concluded that quantitative predictions were not possible (*2*).

The subject of this report is a workshop jointly sponsored by the EPA and WHO on 12–13 December 1995, "UVR-Induced Immune Modulation: Potential Consequences for Infectious, Allergic, and Autoimmune Disease," in Chapel Hill, NC. The aims of the workshop were 1) to review currently available studies relevant to assessing risks associated with UVR effects on the immune system, 2) to identify needs for further research to improve the risk assessment process, and 3) to recommend and prioritize specific research projects for which WHO should actively seek funding. Two of the most problematic areas for risk assessment are extrapolating from immune function data obtained in laboratory rodents to humans, and extrapolating from effects on human immune functions to potential effects on infectious diseases and/or vaccine effectiveness. These issues were addressed in sessions one and two, respectively. Session three dealt with the possibility that UVR immune modulation may impact allergic and autoimmune disease as well.

Session 1: Quantitative comparisons between human and mouse studies: applications to the development of risk assessment models. Dr. Noonan reviewed experimental evidence for dose and wavelength-dependent UVR-induced modulation of contact hypersensitivity (CH) and delayed-type hypersensitivity (DTH) in mice. Suppression of these immune responses appears to play a critical role in the growth of skin cancers and enhances the progression of certain infections in mice. Dose–response data from a study (*3*) of 18 strains of inbred mice demonstrated three phenotypes for suppression of CH (Table 1). The total dose required for immune suppression is much less than that required for skin cancer induction and, unlike cancer induction, is independent of dose–rate and dose fractionation. Dr. Assaf then presented studies done by Cooper et al. (in collaboration with the EPA) showing dose–response curves for UVR-induced suppression of CH in humans [K.D. Cooper, personal communication; (*4*)]. Subjects (ranging from light skinned to heavily pigmented) were grouped according to UVR sensitivity based on minimal erythemal dose, and doses of UVR causing 50% immunosuppression were determined for each skin type (Table 1). These doses could easily be achieved at midday in temperate latitudes under summer sun and were less than that required to achieve 50% suppression in the most sensitive mice in Noonan's studies. Hence, the responses of mice and humans to UVR-induced suppression of CH are quantitatively similar (Table 1). Dr. Selgrade described a parallelogram model (Fig. 1) that has been used to make comparisons between effects in laboratory rodents and humans, and between deficits in immune function and increased susceptibility to disease (*5*). In such models, dose–response data from Drs. Noonan and Assaf would correspond to the upper corners of the parallelogram. Dose–response data on host resistance to infection in mice and the potential for assessing vaccine effectiveness in humans presented in session two would correspond to the lower corners. Quantitative comparisons could then be made between the corners of the parallelogram, which would indicate how well CHS predicts effects on response to infectious disease and how well mouse data predicts human effects.

Session 2: Potential impact of UVR on infectious disease and vaccine effectiveness. Dr. Jeevan reviewed studies in which UVR exposure increased the incidence and/or severity of infection in mice challenged with viral, parasitic, fungal, and bacterial agents. She presented data with *Mycobacterium bovis* BCG (the vaccine strain for tuberculosis) and *M. lepraemurium* (a mouse leprosy model). The UVR dose required for 50% suppression of the DTH response to these two agents (Table 1) resulted in approximately a threefold increase in the number of BCG bacteria in spleen and lymph nodes of infected mice (*6*). Dr. van Loveren described similar studies in rats in which there was a strong relationship between suppression of the *in vitro* lymphoproliferative response to bacterial antigen following *in vivo* UVR exposure and increased susceptibility to challenge with bacteria. Also, he reported a 3.8-fold difference in the dose required to suppress the skin-mixed lymphocyte response by 50% in humans and rats and indicated that his data could be applied in a parallelogram model to predict effects on resistance to bacterial infection in humans. (Table 1) (*7*). Dr. Ward described three opportunities for field studies to assess effects of UVR exposure on vaccine effectiveness in humans. First, vacci-

Address correspondence to MJ.K. Selgrade, MD 92, U.S. Environmental Protection Agency, Research Triangle Park, N.C. 27711 USA.

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nation with BCG is about 50% effective against tuberculosis and is given to most children in developing nations shortly after birth. In some of these same nations, hyperbilirubinemia in newborns is treated by graded solar exposure (containing UVR), usually before BCG vaccination. Children without hyperbilirubinemia are generally protected from the sun. Hence, comparison of subsequent responses to BCG in these two populations would provide an indication of the effect of UVR on vaccine-induced immunity. Second, a study of the influence of season on cellular responses to measles vaccine presents another opportunity when conducted in an area with dramatic seasonal differences in climatic conditions (e.g., Lima, Peru). Third, a comparison of hepatitis B vaccine-induced responses after short-term travel from temperate regions (e.g., Montreal) to the tropics for beach holidays versus other types of low-UVR exposure travel is also feasible. Drs. Duncan and Regan described personal dosimeters, polysulphone badges (*8*), and badges consisting of dried Lambda DNA between layers of ACLAR film (*9*), respectively, which could be used along with radiometric measures of ambient UVR to estimate exposure doses in the studies described by Dr. Ward. Hence, there appear to be opportunities to determine dose–response relationships for effects of UVR on the effectiveness of certain vaccinations.

Session 3: UVR modulation of T-helper (Th) lymphocyte subpopulations: potential consequences for allergic and autoimmune disease. Whereas most of the concern over UVR modulation of the immune system has focused on potential effects on susceptibility to skin cancer and infectious disease, the mechanisms by which UVR modifies immune responses might also result in increased risks associated with allergic and autoimmune disease. Dr. Ullrich described studies in mice that suggest that interleukin-10, released from keratinocytes following UVR exposure, circulates in the blood stream, alters antigen presentation to Th1 cells but not Th2 cells, and results in the suppression of DTH (*10*). Because Th1 and Th2 cells are mutually antagonistic, and because Th2 cells are responsible for immediate-type hypersensitivity to allergens such as dust mites, UVR has the potential to exacerbate allergic disease. Dr. Peden presented information suggesting that Th2 cells have an important role in atopic asthma in humans. Dr. McCauliffe presented information on the effects of UVR on autoimmune disease, particularly systemic lupus erythematosus (SLE). The pathogenesis of sys-

Table 1. UVR dose in millijoules (mJ/cm^2) required to suppress immune responses by 50%: compilation of dose–response data presented by different investigators

Response	Mouse		Human		Rat
	UV sensitivity	ED_{50}	Skin type	ED_{50}	ED_{50}
Contact sensitivity	High (C57BL/6)	220[a]	Fair	90[b]	—
	Intermediate (C3H/HeN)	600[a]	Medium	140[b]	—
	Low (BALB/c)	1,230[a]	Dark	150[b]	—
DTH to MLM	BALB/c	230[c]	—	—	—
DTH to BCG	BALB/c	270[c]	—	—	—
Mixed-skin lymphocyte response	—	—	Mixed	418[d]	108[d]
Lymphocyte proliferation to bacteria	—	—	—	—	680[d]

Abbreviations: ED_{50}, dose causing 50% suppression of immune response; DTH, delayed-type hypersensitivity; MLM, *Mycobacteriium lepraemurium*; BCG, *Mycobacterium bovis*.
[a]Data from Noonan and Hoffman (*3*).
[b]Data from Oberhelman et al. (*4*) and Assaf (unpublished data).
[c]Data from Jeevan and Kripke (*6*).
[d]Data from Van Loveren et al. (*7*).

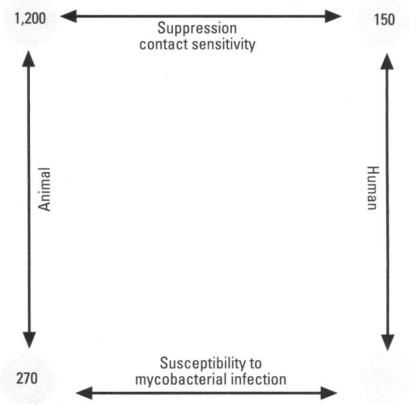

Figure 1. Parallelogram model. Dose (mJ/cm^2) required to suppress contact hypersensitivity by 50% for BALB/c mice from Noonan (*3*) and delayed-type hypersensitivity to *Mycobacterium bovis* from Jeevan (*6*) are indicated in circles on left. Data for suppression of contact sensitivity in most resistant humans [K.D. Cooper, personal communication (*4*)] is represented in upper right corner. Data from vaccine effectiveness study could be used in lower right corner. Factors could then be obtained to describe the relationship between these parameters and would indicate in a quantitative fashion the ability of effects on contact hypersensitivity to predict effects on immune responses to infection and the ability of mouse data to predict human effects.

Meeting Participants

Richard Assaf
Case Western Reserve

Robert Chapman
NHEERL, U.S. EPA

Fernando Diaz
Johns Hopkins School of Public Health

David DeMarini
NHEERL, U.S. EPA

Don Duncan
Johns Hopkins Applied Physics Laboratory

Amminnikutty Jeevan
Formerly with M.D. Anderson Cancer Center

Hillel Koren
NHEERL, U.S. EPA

Robert Luebke
NHEERL, U.S. EPA

Dan McCauliffe
University of North Carolina

Frances Noonan
George Washington University
Medical Center

David Peden
University of North Carolina

Mike Repacholi
World Health Organization

Jim Regan
Florida Institute of Technology

Luis Segura
Asociacion Benefica PRISMA
Lima, Peru

MaryJane Selgrade
NHEERL, U.S. EPA

David Sliney
U.S. Army Environmental Hygiene Agency

Mario Smith
Analytical Sciences

Stephen Ullrich
M.D. Anderson Cancer Center

John Vandenberg
NHEERL, U.S. EPA

Henk van Loveren
RIVM
Bilthoven, The Netherlands

Brian J. Ward
McGill University

Hiroko Yoshida
Florida Institute of Technology

temic autoimmune disease such as SLE appears to be mediated by Th2 cells, in contrast to organ-specific autoimmune diseases (e.g., insulin-dependent diabetes mellitus), where Th1 cells appear to be more important. Hence, UVR has the potential to affect autoimmune diseases in either an adverse or beneficial fashion depending on the disease.

Summary of research needs identified. The group was unanimous in giving highest priority to studying the effects of UVR on vaccine effectiveness in humans. All three studies presented by Dr. Ward would be valuable. However, the proposed studies were ranked in priority as follows 1) BCG, 2) measles, and 3) hepatitis. There was consensus that these studies should incorporate the use of both personal dosimeters and radiometric measurements of ambient UVR in order to obtain dose–response information.

Information on the effects of UVR should be expanded beyond DTH and CH. Other types of immune functions, such as epidermal mixed-lymphocyte reactions and serum cytokine responses, should be assessed in both rodents and humans. This information is needed to characterize the extent of damage to the immune system, provide additional mechanistic information, and provide insights about the types of infections likely to be affected by UVR.

Suppression of CH responses has only been demonstrated in humans following application of the allergen to the site of UVR exposure. Unlike the mouse model, limited attempts to demonstrate effects with application to a distant site have been unsuccessful. However, suppression of the lymphoproliferative response of peripheral blood lymphocytes to herpes simplex virus has been observed following UVR exposure (*11*). Additional work is needed to determine the extent to which systemic suppression of immune responses occurs in humans and under what experimental conditions.

More information is needed on the wavelength dependency of UVR-induced immune suppression. Although some animal studies have been done with narrow bands of UVR, most studies have used broad-spectrum SF 40 sunlamps. There is little information on the action spectrum for human immune suppression. Questions requiring answers include: Is the action spectrum for immune suppression the same for mice and humans? What role does UVA play in immune suppression and are there potential interactions between UVA and UVB? Are data generated with SF lamps similar enough to solar exposure to be useful in making quantitative risk assessments with respect to depletion of stratospheric ozone?

Finally, UVR appears to favor Th2 responses, suggesting that risks associated with common allergies and asthma may be increased by UVR exposure. This possibility has not been explored. Also, although UVR is known to exacerbate certain autoimmune diseases, the link with UVR-modulation of the immune system has not been made. The group felt that these risks could best be addressed using animal models. Should these studies suggest that UVR can enhance allergic or autoimmune disease, then human studies could be planned to assess these risks.

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